The Need for a Prophylactic Gastrojejunostomy for Unresectable Periampullary Cancer

A Prospective Randomized Multicenter Trial With Special Focus on Assessment of Quality of Life

N. Tjarda Van Heek, MD, Steve M.M. De Castro, MS,* Casper H. van Eijck, MD,† Rutger C.I. van Geenen, MD,‡ Eric J. Hesselink, MD,§ Paul J. Breslau, MD,‖ T.C. Khe Tran, MD,† Geert Kazemier, MD,† Mechteld R.M. Visser, PhD,¶ Olivier R.C. Busch, MD,* Hugo Obertop, MD,* and Dirk J. Gouma, MD**

Objective: To evaluate the effect of a prophylactic gastrojejunostomy on the development of gastric outlet obstruction and quality of life in patients with unresectable periampullary cancer found during explorative laparotomy.

Summary Background Data: Several studies, including one randomized trial, propagate to perform a prophylactic gastrojejunostomy routinely in patients with periampullary cancer found to be unresectable during laparotomy. Others suggest an increase of postoperative complications. Controversy still exists in general surgical practice if a double bypass should be performed routinely in these patients.

Methods: Between December 1998 and March 2002, patients with a periampullary carcinoma who were found to be unresectable during exploration were randomized to receive a double bypass (hepaticojejunostomy and a retrocolic gastrojejunostomy) or a single bypass (hepaticojejunostomy). Randomization was stratified for center and presence of metastases. Patients with gastrointestinal obstruction and patients treated endoscopically for more than 3 months were excluded. Primary endpoints were development of clinical gastric outlet obstruction and surgical intervention for gastric outlet obstruction. Secondary endpoints were mortality, morbidity, hospital stay, survival, and quality of life, measured prospectively by the EORTC-C30 and Pan26 questionnaires. It was decided to perform an interim analysis after inclusion of 50% of the patients (n = 70).

Results: Five of the 70 patients randomized were lost to follow-up. From the remaining 65 patients, 36 patients underwent a double and 29 a single bypass. There were no differences in patient demographics, preoperative symptoms, and surgical findings between the groups. Clinical symptoms of gastric outlet obstruction were found in 2 of the 36 patients (5.5%) with a double bypass, and in 12 of the 29 patients (41.4%) with a single bypass ($P = 0.001$). In the double bypass group, one patient (2.8%) and in the single bypass group 6 patients (20.7%) required (re-)gastrojejunostomy during follow-up ($P = 0.04$). The absolute risk reduction for reoperation in the double bypass group was 18%, and the numbers needed to treat was 6. Postoperative morbidity rates, including delayed gastric emptying, were 31% in the double versus 28% in the single bypass group ($P = 0.12$). Median postoperative length of stay was 11 days (range 4–76 days) in the double versus 9 days (range 6–20 days) in the single bypass group ($P = 0.06$); median survival was 7.2 months in the double versus 8.4 months in the single bypass group ($P = 0.15$). No differences were found in the quality of life between both groups. After surgery most quality of life scores deteriorated temporarily and were restored to their baseline score (t = -1) within 4 months.

Conclusions: Prophylactic gastrojejunostomy significantly decreases the incidence of gastric outlet obstruction without increasing complication rates. There were no differences in quality of life between the two groups. Together with the previous randomized trial from the Hopkins group, this study provides sufficient evidence to state that a double bypass consisting of a hepaticojejunostomy and a prophylactic gastrojejunostomy is preferable to a single bypass consisting of only a hepaticojejunostomy in patients undergoing surgical palliation for unresectable periampullary carcinoma. Therefore, the trial was stopped earlier than planned.

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From the *Department of Surgery and ¶Medical Psychology, Academic Medical Center, Amsterdam; ‡Department of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam; †University Hospital Dijkzigt, Rotterdam; §Hospital Gelre Apeldoorn, Apeldoorn; and ‖Hospital Rode Kruis, The Hague, The Netherlands.

Reprints: D.J. Gouma, MD, Department of Surgery, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. E-mail: d.j.gouma@amc.uva.nl.

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Of the patients with periampullary tumors who undergo exploratory surgery with the intention to perform a pancreaticoduodenectomy, 25% to 75% are found to have unresectable disease.[1–3] Appropriate palliation of the main

symptoms obstructive jaundice, duodenal obstruction, and pain is of major importance in these patients.[4]

Since 70% of the patients with periampullary carcinoma present with jaundice,[1] adequate biliary drainage is essential for palliation.[5,6] Nonsurgical options include the percutaneous or endoscopic insertion of endoprostheses. Surgical options include internal drainage by means of a biliodigestive bypass, which is suggested to be treatment of choice in patients in a reasonable to good physical condition and a life expectancy of at least 3 to 6 months.[4,7] However, especially after relatively long survival, 10% to 20% of patients develop gastroduodenal obstruction after a biliary-digestive bypass alone, as demonstrated by retrospective reviews of surgical series.[1,8,9] In a recent prospective randomized study, it was even shown that patients with metastases found during explorative laparotomy in patients scheduled for resection should preferably be treated with a surgical bypass instead of stenting.[10] To prevent gastroduodenal obstruction, a prophylactic gastroenterostomy has been advised during the same surgical procedure. In a prospective randomized controlled trial from the Johns Hopkins group published shortly after starting the present trial, it was concluded that a gastrojejunostomy should be performed routinely when a patient is undergoing surgical palliation for unresectable periampullary carcinoma.[11]

However, it can be questioned whether results from one center of excellence in a selected group of patients can be generalized.[3,12] Others showed disadvantages of adding a gastrojejunostomy to the operation.[7,13] In a study from The Netherlands, it was shown that a double bypass did increase morbidity and even mortality.[14] Another well-known complication after prophylactic gastrojejunostomy is delayed gastric emptying, varying from 2%[11] to 14%, which might increase the complication rate after a double bypass.[13] Therefore, a double bypass is not yet generally accepted as standard treatment.

Quality of life (QoL) was not addressed from a patient perspective by means of questionnaires in the trial from Hopkins.[11] Health-related QoL may be informative, especially in trials of advanced-stage cancer comparing different palliative treatments with limited effects on survival gain and tumor response.[15–17] There is accumulating evidence to suggest that QoL scores have prognostic value.[17] We have therefore conducted this randomized study with special focus on assessment of QoL. The aim was to evaluate the effect of a prophylactic gastrojejunostomy in patients undergoing biliodigestive anastomosis for unresectable periampullary carcinoma in a multicenter trial. Because the results from the previous mentioned randomized controlled trial from the Hopkins group were published shortly after the start of the present study,[11] it was decided to perform an interim analysis after the inclusion of 50% of the patients (n = 70).

PATIENTS AND METHODS

Patients

Patients with unresectable disease found during surgical exploration with the intention to perform a resection in the Academic Medical Center Amsterdam, the University Hospital Dijkzigt in Rotterdam, and two general Dutch hospitals between December 1998 and March 2002, were considered for inclusion in this trial. After perioperative finding of metastases or ingrowth in major visceral vessels they were randomized for a double bypass (hepaticojejunostomy and a retrocolic gastrojejunostomy) or a single bypass (hepaticojejunostomy alone). Randomization was centralized in the Academic Medical Center Amsterdam, with stratification for center and the presence of metastases.

The primary end point was signs and symptoms of gastric outlet obstruction (GOO) and surgical intervention for GOO. Secondary endpoints were mortality, morbidity including postoperative delayed gastric emptying, hospital stay, survival, and QoL. Inclusion criteria were unresectable periampullary cancer and biliary obstruction during explorative laparotomy. Exclusion criteria were upper gastrointestinal surgery in history, endoscopic treatment of longer than 3 months, presentation with gastric or duodenal obstruction, no cytologic or histologic prove of malignancy, and tumor-positive ascites. This study was approved by the Medical Ethical Committees of the Academic Medical Center Amsterdam and by the three other centers involved. Patients with a periampullary tumor who were scheduled to undergo an exploratory laparotomy with the intention to perform a pancreaticoduodenectomy were asked written informed consent in the four participating centers.

The sample size was calculated based on data from the literature. Between 20% and 30% of the patients will develop GOO after biliodigestive bypass for unresectable periampullary cancer,[9,18] whereas approximately 7% of the patients that receive a biliodigestive bypass and a prophylactic gastrojejunostomy for unresectable periampullary cancer will develop GOO as reported previously.[1,13] With an $\alpha = 0.05$ and a power of 0.8 ($\beta = 0.2$), the number of patients needed for each group is 62. Assuming a dropout of 10%, the sample size is 140. Because the randomized controlled trial of the Hopkins group was published shortly after the start of this study demonstrating a significant lower incidence of late GOO in patients with a prophylactic gastrojejunostomy,[11] there was an extensive discussion among the participating centers if the trial should be continued. It was decided to continue but to perform an interim analysis at 50% inclusion of the patients (n = 70) to decide whether continuing inclusion was justifiable.

Definitions

The term periampullary tumors used in this study comprised pancreatic carcinoma, bile duct carcinoma, and amp-

ullary carcinoma. Unresectable cancer was defined as pathologically proven local invasion of major visceral vessels or metastases shown during explorative surgery. Biliary obstruction was defined as clinical jaundice with impaired liver function (more than 2 times the normal range). GOO was defined as clinical symptoms of obstruction, such as nausea and vomiting, in combination with radiologic or endoscopic proof of gastric retention or stenosis. Delayed gastric emptying (DGE) was defined as stomach drainage for longer than 10 days postoperatively or intolerance for normal food intake for longer than 2 weeks postoperatively, as reported previously.[19]

Surgical Procedure

Patients were randomized during surgery after the surgeon found local unresectability or metastases without the presence of imminent duodenal obstruction. Patients received either a retrocolic gastrojejunostomy or no gastrojejunostomy. A hepaticojejunostomy, cholecystectomy, and chemical splanchnicectomy with 50% ethanol were performed routinely. Feeding jejunostomies were only used in a few patients (<10%) with severe malnutrition. Histologic confirmation of the diagnosis was obtained in all patients. Postoperative chemotherapy and/or radiotherapy was used selectively based on the recommendations of a multidisciplinary team from the different hospitals and the patient's preference.

Data Collection

Data were collected prospectively on all patients, including demographics, history, physical examination, surgical findings, and outpatient clinical information. Data collection and follow-up were completed through December 2002 on all patients, based on forms filled in during regularly scheduled visits at the outpatient clinic and interviews by telephone with the general physician or the patient's family.

QoL

For prospective measurement of QoL, the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30, version 2.0, EORTC Study Group on Quality of Life, Brussels, Belgium)[20] and the pancreatic cancer module (QLQ-PAN26)[21] were used. The validated EORTC QLQ-C30 questionnaire is developed to assess the health-related QoL of cancer patients participating in international clinical trials.[21] It comprises 30 items relating to symptoms, physical status, working ability, and emotional, cognitive, and social functioning, as well as a global QoL scale. The validity has been shown previously.[20,22–24] The QLQ-PAN26 is a disease-specific module designed to administer together with the general QLQ-C30. It can be used for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation, or palliative chemotherapy.[25] This model comprises 26 questions assessing pain, dietary changes, altered bowel habit, related emotional problems, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes). These two questionnaires were prospectively assessed at different time points during the study. Baseline measurement (t = -1) was performed after admission in the hospital on the day before surgery. The first postoperative questionnaire was filled in on the day of discharge (t = 0). Following questionnaires were sent monthly to the patients at home and returned by mail (t = 1, 2, 3. . .).

A hypothesis was formulated concerning the scales most likely to reveal an effect of two major endpoints GOO and DGE, and most likely to show a potential difference between both groups. We assumed that the global health status, the physical and emotional functioning, and the pain score of the QLQ-C30, together with all gastrointestinal symptom scales of both the QLQ-C30 and the QLQ-Pan26 would give appropriate information. For this last purpose, an overall digestive symptoms scale including the following scales was created including nausea and vomiting, appetite loss, constipation, and diarrhea from the QLQ-C30, as well as digestive, altered bowel habits, flatulence, and gastrointestinal symptoms from the QLQ-Pan26.

Statistical Analysis

Statistics were performed using the SPSS Base 11.0 for Windows Statistical Software Package (SPSS, Chicago, IL). All results are given as mean (SD) or median and ranges. Differences between the two groups were compared using the Fisher exact test, and differences between means were compared using the Student *t* test. Length of survival in the two groups was compared using the log-rank test. Statistical significance was set at $P < 0.05$.

Standard scoring algorithms were followed for QLQ-C30 and QLQ-Pan26.[26] We performed two different analyses. In the first analysis, we used the available data only without imputing missing data. In the second analysis, we adopted an imputation technique carrying the last QoL value forward to the next occasion. All scores were linearly converted to a scale of 0 to 100. The nonimputed QoL scales were presented graphically for the postoperative phase up to 12 months after date of surgery. To investigate whether QoL differed for both groups shortly before death, an analysis was performed as presented in the studies by Morris, in which death was considered time point 0 and the questionnaires before death were renamed as last before death, second last before death, and so on.[27,28] The mean score, SD, and comparison of the two groups were calculated for each scale at each time point.

RESULTS

Study Population

Of the 70 patients randomized at time of the interim analysis, pathology was revised in two patients and three

TABLE 1. Patient Demographics and Preoperative and Perioperative Findings

	Double Bypass (N = 36)	Single Bypass (N = 29)	*P*
Inclusion [no. (%)]			
Academic centers (n = 2)	28 (78)	24 (83)	0.44
General centers (n = 2)	8 (22)	5 (17)	
Age (yr)	63 ± 9	65 ± 8	0.28
Gender [no. (%)]			
Male	24 (67)	11 (38)	0.026
Female	12 (33)	18 (62)	
Preoperative symptoms [no. (%)]			
Nausea / vomiting*	10 (28)	7 (24)	0.74
Abdominal pain	18 (50)	15 (52)	0.89
Weight loss	24 (67)	17 (59)	0.36
Tumor location [no. (%)]			
Pancreatic head	32 (89)	25 (86)	0.74
Distal common bile duct	4 (11)	2 (7)	0.68
Ampulla	—	2 (7)	0.20
Unresectability [no. (%)]			
Local vascular invasion	19 (53)	15 (52)	1.0
Metastases	16 (44)	13 (45)	1.0
Both	1 (3)	1 (3)	1.0

*Preoperative symptoms of nausea and vomiting were not caused by gastric outlet obstruction.

patients were lost to follow-up. In one patient, definite pathology revealed a benign tumor. In the other patient, revision of the frozen section from a liver biopsy taken during explorative laparotomy revealed active inflammation in stead of adenocarcinoma, and a pylorus preserving pancreaticoduodenectomy was performed subsequently. From the remaining 65 patients, 36 patients (55%) were treated by a double bypass and 29 patients (45%) by a single bypass. The two groups were comparable for patient demographics, preoperative and perioperative findings, but not for gender (Table 1). More men than women received a double bypass for unresectable periampullary cancer, while it appeared to be the opposite in the single bypass group ($P = 0.026$). The mean age in both groups was not different; obstructive jaundice was the most common preoperative symptom with 78% in the double bypass group, and 79% in the single bypass group.

Based on preoperative evaluation and surgical findings, the head of the pancreas was the predominant site of origin of the tumor: 89% of the tumors in the double, and 86% of the tumors in the single bypass group. Since randomization took place for the presence of metastases, the reason for unresectability was equally divided among both groups (Table 1).

Short-term Outcome

Mortality, morbidity, and length of hospital stay for both treatment groups are listed in Table 2. There were no perioperative deaths. A 72-year-old man died in the hospital 24 days after the double bypass procedure. He had been suffering for 3 weeks from iatrogenic bleeding and subsequent intra-abdominal abscesses after a staging laparoscopy before exploration and a bypass procedure were performed.

At least one complication was found in 11 patients (31%) after double bypass and in 8 patients (28%) after single bypass. Delayed gastric emptying was the most frequent complication (17%) after double bypass, but only seen in one patient (3%) after single bypass ($P = 0.12$). The incidence of biliary and gastrojejunal anastomotic leak was the same in both groups. The median postoperative length of stay in hospital was 11 days4–76 in the double bypass group, and 9 days$^{6-20}$ in the single bypass group ($P = 0.06$).

Survival and Long-term Outcome

There was no significant difference in the median survival between the double and the single bypass group: 7.2 and 8.4 months, respectively ($P = 0.15$) (Fig. 1) (Table 3).

During follow-up clinical GOO was diagnosed in 2 of the 36 patients (5.5%) after double bypass, and in 12 of the 29 patients (41.4%) after single bypass ($P = 0.001$). After

TABLE 2. Short-term Outcome, Length of Hospital Stay, and Adjuvant Therapy

	Double Bypass (N = 36)	Single Bypass (N = 29)	*P*
Mortality			
In-hospital [no. (%)]	1 (3)	0	1.0
Morbidity [no. (%)]			
Any complication	11 (31)	8 (28)	0.79
Wound infection	3 (8)	1 (3)	0.62
Biliary anastomotic leakage	1 (3)	1 (3)	1.0
GI leakage	1 (3)	1 (3)	1.0
Pulmonary	1 (3)	2 (7)	0.59
Cardiac	4 (11)	2 (7)	0.68
Intra-abdominal bleeding	0	1 (3)	0.45
Delayed gastric emptying	6 (17)	1 (3)	0.12
Hospital stay (days)			
Median	11	9	0.06
Range	4–76	6–20	
Adjuvant therapy [no. (%)]			
Chemotherapy and radiotherapy	14 (39)	12 (41)	1.0
Chemotherapy	4 (11)	3 (10)	
Radiotherapy	1 (3)	1 (4)	
None	17 (47)	13 (45)	

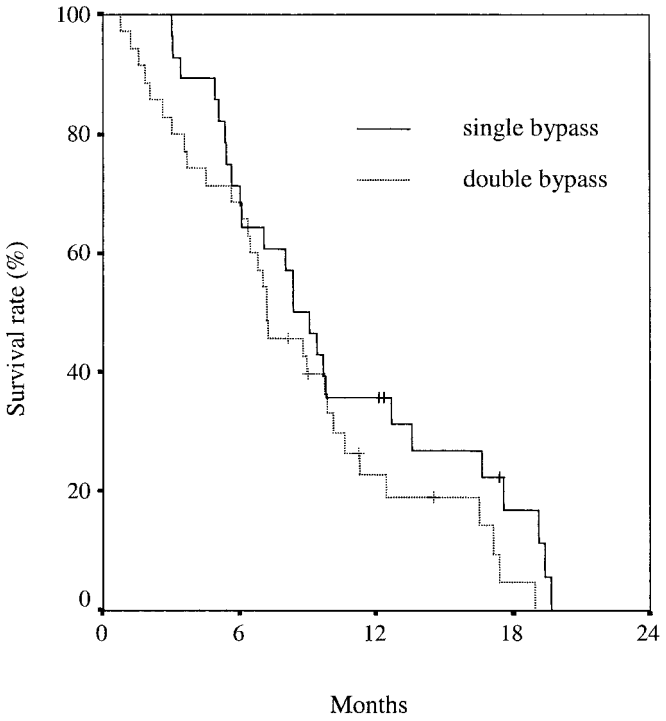

FIGURE 1. Kaplan-Meier survival curve for all included patients (N = 65) with periampullary carcinoma found to be unresectable during explorative laparotomy. A double bypass was performed in 36 patients with a median survival of 7.2 months,[1–19] and a single bypass was performed in 29 patients with a mean survival of 8.5 months[3–20] (P = not significant).

double bypass one patient with GOO (2.8%) underwent relaparotomy and revision of the gastrojejunostomy. After single bypass 6 of the 12 patients with GOO (20.7%) underwent relaparotomy and a gastrojejunostomy was performed ($P = 0.04$) (Table 3). The median time interval between initial exploration and late gastrojejunostomy was 3.5 months. Absolute risk reduction for reoperation by performing a double bypass was 18%, and the numbers needed to treat was 6.

Quality of Life

Compliance with questionnaire completion was comparable in the double and the single bypass group. The compliance rate in both groups was >90% in the first 4 months after surgery and decreased to 75% in the last 2 months of the terminal phase. Outcomes of QoL assessment were independent of the analysis used. The QoL scales based on nonimputed data are shown in Figure 2 by means of a graph with error bar (confidence interval for mean 95%) for each scale. Overall, no major differences were seen in QoL between the two surgical treatment groups. Patients in both groups showed a similar course in the scores for all scales and did not differ from each other significantly at most points in time. On the day of discharge (t = 0), both groups showed a significant decrease in all functional scales except the physical functioning compared with the preoperative status. The symptom variables pain and digestive symptoms were significantly more pronounced after both surgical procedures. Overall, the QoL scores were stable over the course of the study for patients in both groups. All scales came back to their original baseline score (t = -1) within 4 months and remained so throughout follow-up.

In Figure 3, the terminal phase of the last 6 months is represented in a graph for the five subscales of QoL in both groups. The time of death is on the right side of the graph. No differences in QoL were seen in the months before death between the two groups. In both groups the global health status and emotional functioning score decreased rapidly during the last 2 months before death.

DISCUSSION

The outcome of this prospective randomized controlled trial gives further support to the strategy to routinely perform a retrocolic gastrojejunostomy in patients undergoing a palliative biliodigestive bypass for unresectable periampullary cancer found during explorative laparotomy. Prophylactic gastrojejunostomy added to a hepaticojejunostomy significantly decreases the incidence of late GOO and relaparotomies without increasing the incidence of postoperative complications. Patients do not report differences in QoL after receiving a double or a single bypass. Hospital stay was slightly longer for the patients with a double bypass (11 days) than for the patients with a single bypass (9 days), although not statistically significant ($P = 0.06$). We can conclude from this study that patients who are found to have an unresectable tumor at laparotomy for periampullary cancer are preferably treated by a hepaticojejunostomy and prophylactic gastrojejunostomy compared with a hepaticojejunostomy alone.

In patients with unresectable periampullary cancer palliation of obstructive jaundice, duodenal obstruction and pain are of primary importance, preferably with a short hospital stay, maximal survival, and optimal QoL.[4,5] Palliation of obstructive jaundice by nonsurgical techniques is the treatment of choice when unresectable cancer is already found during diagnostic workup, particularly in patients with an expected short survival. Endoscopic and percutaneous biliary stenting are successful modalities, although recurrent cholangitis due to stent occlusion is a well-known problem despite all efforts to prevent this very common complication.[29–32] Fit patients will benefit from palliative surgery that allows long-lasting biliary drainage,[5,33] and biliary bypass procedures can be undertaken nowadays with acceptable rates of morbidity and mortality.[34–36] In a trial on diagnostic laparoscopy performed before the present study, surgical palliation proved to be superior to stenting in patients with an unresectable tumor found during laparotomy with the intention to perform a

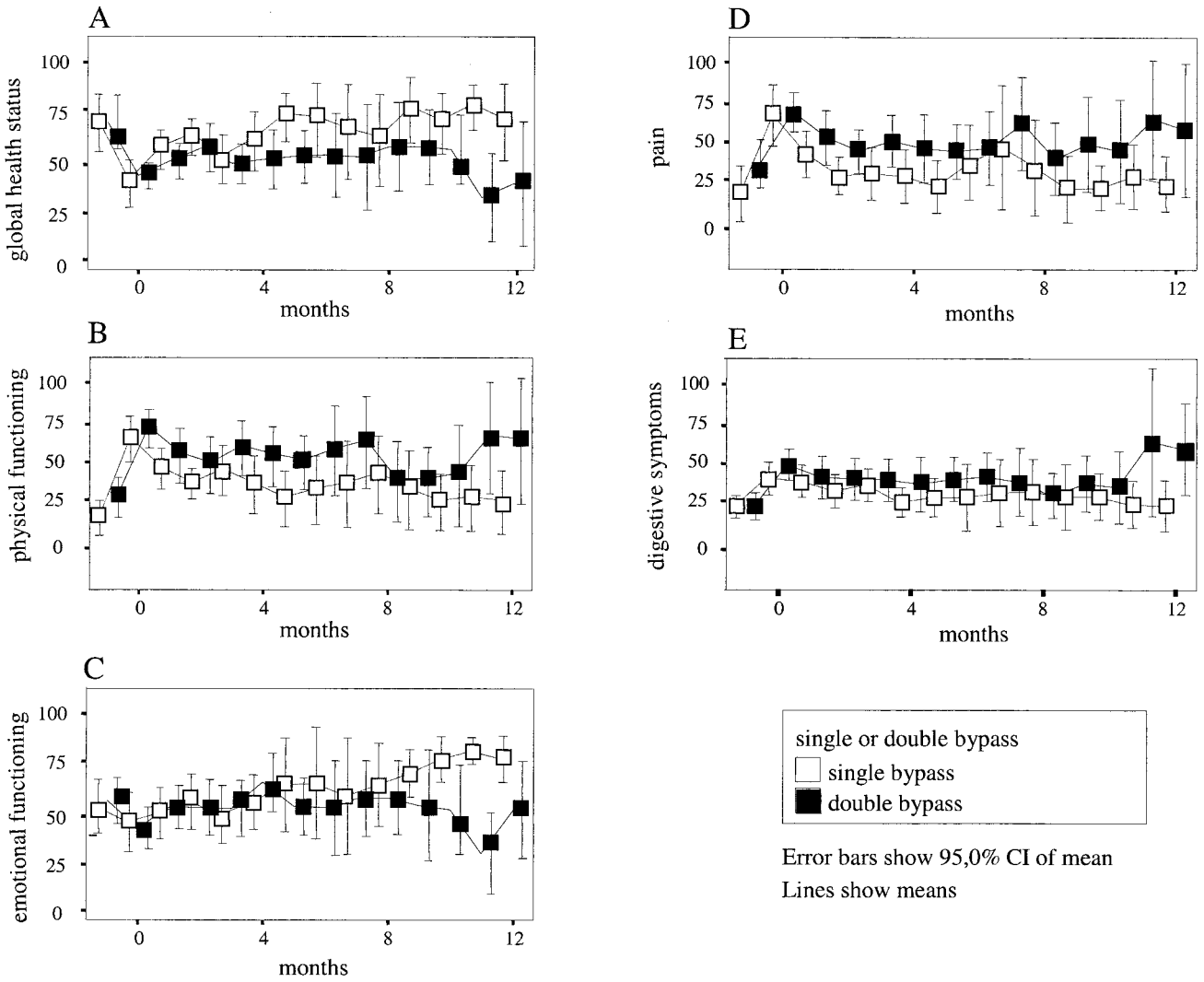

FIGURE 2. QoL graphs representing the 12 months after surgery of the patients randomized to receive a double or a single bypass. Left side of graph represents time of operation. The nonimputated data of the following subscales are presented: A: Global health status. B: Physical functioning. C: Emotional functioning. D: Pain. E: Digestive symptoms.

resection.[10] To add a "prophylactic" gastrojejunostomy to the biliary bypass procedure is based on the relatively high incidence of GOO that has been reported during follow-up.[37,38] The reluctance to perform a prophylactic gastroenterostomy routinely is based on the occurrence of additional postoperative complications; DGE and gastrointestinal bleeding have been reported.[39,40] In the principle of "non nocere" surgery should have a minimal risk of postoperative complications, especially in these patients with palliative treatment.

Earlier studies on surgical gastroenterostomy reported postoperative morbidity and mortality rates from 5% to 41% and 11% to 33%, respectively.[14] In one study, it was stated that the need for a gastrojejunostomy due to GOO was associated with a poor outcome and had little role in the management of patients with pancreatic cancer.[39] However, death was their only end point.[39] In a more recent study, it has been suggested that patients with unresectable periampullary cancer do not survive long enough to develop a gastrointestinal obstruction and there would be no need for a prophylactic gastrojejunostomy.[41] In a retrospective study from the Memorial Sloan Kettering Cancer Center, the perioperative morbidity rate increased significantly without prolonging survival by the addition of a prophylactic gastric bypass.[42]

More recently, proponents of the prophylactic gastrojejunostomy observed that the concomitant biliary and gastric bypass did not increase the operative morbidity and mortality.[11,34,36,43–45] Also, mortality of subsequent gastric bypass added to initial single bypass could be as high as 25%, whereas the incidence of subsequent GOO in those without gastric bypass was 10%.[46]

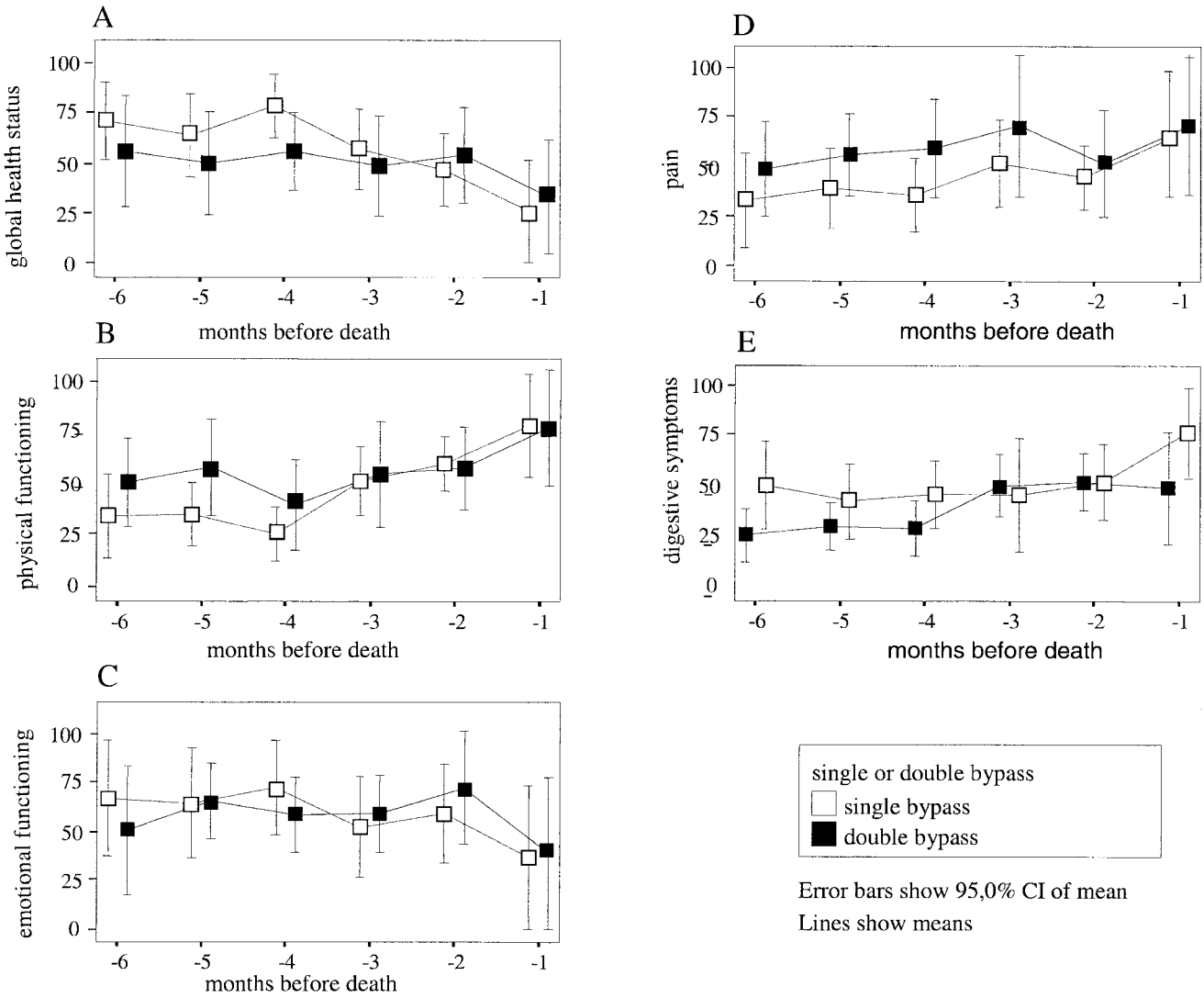

FIGURE 3. QoL graphs representing the terminal phase (6 months before death) of the patients randomized to receive a double or a single bypass. Right side of the graph represents death. The nonimputated data of the following subscales are presented: A: Global health status. B: Physical functioning. C: Emotional functioning. D: Pain. E: Digestive symptoms.

The Johns Hopkins group was the first to show the benefits of a routinely performed prophylactic gastrojejunostomy in a randomized trial,[11] but controversy still exists in general surgical practice. The fact that the study was performed in a highly specialized referral center in the United States is probably a reason to doubt whether the findings in a selected group of referred patients can be generalized.[3] The relatively high incidence of patients with tumors located in the uncinate process could also influence the occurrence of GOO because of their location related to the duodenum. In the present multicenter trial, 42% suffered from symptoms of GOO and 21% of the patients after a single bypass and 3% of the patients after a double bypass had to undergo a gastrojejunostomy in a later phase of their life. It would have been ideal to let an independent observer decide whether the patient needed a relaparotomy for GOO; however, this was not feasible, and the decision was made by the local surgeons. Although late GOO could be the result of functional disturbance rather than an organic obstruction, functional outcome is the most important outcome in patients undergoing palliative surgery for periampullary cancer. Six patients needed a double bypass to prevent one patient from undergoing a reoperation (absolute risk reduction = 18% and numbers needed to treat = 6). Operative morbidity and mortality were not significantly different. The limited, not significant, differences in survival were probably due to the male/female ratio, a well-known risk factor.[47]

As discussed earlier, we decided immediately after the start of this study to perform an interim analysis after inclu-

sion of 50% of the patients (n = 70) because of the publication of the first randomized trial from the Johns Hopkins Hospital.[11] At that time (1999), there was even a discussion if this second trial should be performed or stopped immediately. There was agreement to continue, to perform an interim analysis, and to stop if a significant difference was found in the primary end point (GOO) toward the same direction as the Hopkins trial. Because the outcome of this interim analysis was comparable with the outcome of that trial, the participating centers decided to discontinue the trial accordingly.

A statistician (Professor P.M. Bossuyt, head of the department of Clinical Epidemiology) was consulted to discuss the proposal of stopping the trial. Regarding the decision in 1999 to perform an interim analysis and the significant difference in primary end point comparable to the first randomized trial, he considered stopping the trial justified, realizing that this would reduce the "strength" of the trial and could introduce a type II error. An important aspect of palliative surgery is the quality of the remaining life.[16] Only limited data are available with respect to QoL assessment in patients after surgical palliation for unresectable periampullary cancer. No prospective study has been performed as yet in which QoL was estimated in patients who were treated by two different surgical palliative strategies using a standardized questionnaire. Health-related QoL assessment seeks to measure the impact of the disease process on the physical, psychologic, and social aspects of the person's life and feeling of well-being.[48]

The EORT QLQ-C30 was used as a valid and reliable instrument for assessing overall QoL in cancer patients,[49] and the QLQ-Pan26 as a disease-specific questionnaire.[25] A definite conclusion from this trial is that no major differences were found in the various subscales of QoL between patients after a double bypass and after a single bypass. Both groups showed a temporary decrease in global health status and emotional functioning, and a temporary postoperative increase in pain and digestive symptoms. In the terminal phase 2 months before death, a decrease on most QoL scales was seen, as could be expected, but no differences were found between the two groups either. Recovery after both types of surgery was the same. It might be that a negative effect of GOO in the single bypass group is compensated by a relatively early surgical intervention and that other aspects (end stage of disease) influenced QoL more than symptoms.

There are some well-known difficulties associated with the analysis of QoL data in a progressive disease, mostly because of the multidimensional and longitudinal nature of QoL data.[50] In many trials like this one, analysis is complex due to attrition caused by the reduction of patients numbers through death and missing data values due to patient noncompliance at the end stage of the disease.[51] In our study, many data were missing in the postoperative follow-up of 12 months due to attrition because the median survival was 8 months. We chose to report the available nonimputed data and not the imputed nonignorable missing data because both analyses revealed the same outcome. Our strategy probably reports an overestimation of QoL toward the end of life, since a number of patients were too weak to fill in the questionnaires at that point. Mentioned restrictions, however, are not of great importance for the QoL assessment of both groups because the aim was to identify differences between two palliative treatments.

TABLE 3. Long-term Outcome and Survival

	Double Bypass (N = 36)	Single Bypass (N = 29)	*P*
Gastric outlet obstruction [no. (%)]			
Clinical	2 (6)	12 (41)	0.001
Reoperation needed	1 (3)	6 (21)	0.04
Survival (mo)			
Median	7.2	8.4	0.15
Range	1–19	3–20	

CONCLUSION

This prospective randomized controlled trial confirms that in patients with periampullary cancer found to be unresectable during explorative laparotomy with the intention to perform a resection, a double bypass consisting of a hepaticojejunostomy and a prophylactic gastrojejunostomy is preferable to a single bypass consisting of only a hepaticojejunostomy. The need for reoperation for GOO was significantly reduced without increasing complication rates. The early postoperative decreased QoL was not additionally jeopardized by the extra bypass. Therefore, the trial was stopped earlier than planned.

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Discussion

DR. A. FINGERHUT: Thank you for this wonderful paper and thank you for giving me the privilege of reading the manuscript before the conference.

I start my commentary with two citations: one is from Pribram in 1923, who has been cited to say that "gastroenterostomy is not an operation, it is a disease." You have shown that this is not always the case. The second is from Jean Marie Hay who said, "controlled trials have to be controlled." And this is what you have done. Congratulations.

I have two slides, the first in which you can see in the first column a list of nine nonrandomized but mostly controlled studies that have dealt with this topic in the literature; the second column is the controlled study from Baltimore which you mentioned and then, in the third, the results of your paper. As you have already said, one difference between your study and the study from Baltimore is that they randomized whether to perform gastrojejunostomy or not, but not the biliary anastomosis. It is surprising to see that 20% of their patients did not have a biliary operation. But other than that, your results are very comparable. The only thing I would like to comment on is, and I hope that our president will not take offense, that as the Baltimore study is a mono-institutional study coming from a highly specialized unit, and that yours is a multicenter study, the patients you are operating on might not be the same, and therefore, patient selection, and not only patient volume, could explain part of the (good) results. This is suggested here in another paper, also from the Baltimore group and published by Sosa, which shows that there are differences in the patients that are operated on in high- and low-volume centers in the state of Maryland. As you can see in my third slide, there is a statistically significant difference in the proportion of patients who are younger, more males, more Caucasians, more without comorbidity, those coming from out of state, those who have better insurance treated in the high-volume centers. We have already written about the possibility of patient selection in highly specialized centers.

This leads to my first question. As yours was a multicenter study, did you look to see if there was any center effect in outcome between the academic part and the nonacademic part of the hospitals involved? In other words, can the results be generalized to the overall population of surgeons who were doing these operations?

Second question: Of the 14 patients that had a complication, 2 were in the double derivation group, 12 in the single. About half of these patients were operated on, half were not. What was the basis for your decision to operate or not, because that was one of your main end-points? Last question: in your paper, you said that quality of life might have a prognostic value; however, you have not shown any difference here. Do you still believe that it has a prognostic value?

Thank you for presenting a very interesting study, and I hope that this paper will be published.

Dr. N.T. van Heek: Thank you, Professor Fingerhut for your kind remarks and questions.

I hope you do realize that the paper in which people called gastrojejunostomy a disease was published 80 years ago. To comment on your first question, we did not look for differences between the general and the academic hospitals. As you can see, 9 of the 36 patients in the double bypass group versus 8 of the 29 patients in the single bypass group were randomized in general hospitals. These numbers are too small to perform a subanalysis. However, I would like to emphasize that the operative procedure was standardized in all hospitals.

In your second question, you asked why some patients with GOO after a bypass procedure did not undergo a relaparotomy. Only a minority of the patients was treated conservatively for GOO because their clinical condition was too bad to undergo surgery.

Concerning your last question: it is stated in the literature that quality of life could have a prognostic value. We all do realize that the quality rather than the "quantity" of life is essential in palliative surgery. Although we also expected to see a difference in quality of life in favor of the double bypass, in particular for digestive symptoms, remarkably we were not able to show any difference, even in the specific subscales.

Dr. P. Neuhaus: In your abstract you referred to pancreatic head cancer; in your presentation indeed you talk about periampullary cancer. These are two different entities, and you will rarely encounter a vascular invasion to the mesenteric vein in periampullary cancers. My questions are: What was the average size of the tumor? (This can be important for the decision and prophylactic gastrojejunostomy.) Then, since 31 patients had metastases and 34 patients local ingrowths, I wonder how many pancreatic cancer patients you had at all and what the percentage of resectable patients is. Third, if the number of inoperable patients is very high, I would like to ask your opinion on preoperative laparoscopic assessment of operability and your procedures with those operations found inoperable on laparoscopy, because those patients in our hands almost never have an open abdominal operation.

Dr. N.T. van Heek: Thank you, Professor Neuhaus, for your questions.

The nomenclature of tumors in the pancreatic region (periampullary, peripancreatic, pancreatic head) is confusing indeed. In the present series, 78% of the patients had pancreatic head carcinoma, the others either ampullary or distal bile duct carcinoma, together defined as peripancreatic carcinoma. I realize that obstruction is less often seen in the latter patients, but looking at the trial from Hopkins, they also included patients with tumors in the uncinate process, which are more likely to give GOO in a later phase.

We stratified for the presence of metastases: 31 patients were unresectable due to metastases, 34 due to local ingrowth. Unfortunately, I do not have details on the number of patients that underwent a resection during the period of inclusion in all participating centers. In our institution (AMC), roughly 70% of the patients with a periampullary tumor with an attempt to perform a curative resection will undergo a resection.

Concerning your question on preoperative laparoscopic assessment: a previous study from our institution, published in *Annals of Surgery* (January 2003), showed that preoperative laparoscopy should not be performed routinely because hospital free survival was longer after bypass surgery compared with laparoscopy and subsequent endoscopic stenting.

DR. L. FERNANDEZ-CRUZ: I enjoyed the presentation very much. When the study was planned based on data from literature, 140 patients were planned for inclusion in this study. However, during the investigation the authors decided to perform an interim analysis with only 70 patients to decide whether continuing inclusion was justifiable. In fact, they stopped the study with only 36 patients treated by a double bypass and 29 patients treated by a single bypass. The main reason for not reaching 140 patients was that the outcome was comparable to the Baltimore study. Pancreatic cancer patients are suffering not only from organic but also from functional disturbances. I believe that in a study that deals with these patients the number is crucial.

Therefore, the statistical power of this analysis should be taken with caution.

In the study not all patients had jaundice (78% of patients in the double bypass group and 79% in the single bypass group). What was the indication for biliary bypass in patients without bile retention?

Although differences were not statistically significant, morbidity in the double bypass group was higher than in the single bypass group (concerning hospital stay, wound infection, and delayed gastric emptying). Even survival was lower in the double bypass group.

The conclusion of the study is that the risk for reoperation can be significantly reduced if a double bypass is to be performed. Gastric outlet obstruction was diagnosed in 12 patients in the single bypass group. Six of these were operated on. There are no data concerning the other six. I believe that the conclusion is based on a very small group of patients.

DR. N.T. VAN HEEK: Thank you for your questions. Our primary end point was symptoms of GOO and the need for reoperation for GOO. The patients that underwent a single bypass developed significantly more symptoms of GOO and also needed significantly more reintervention. None of the other parameters we studied showed a significant difference between both groups. DGE occurred (not significantly) more often in the double bypass group than in the single bypass group, and the hospital stay was correspondingly longer. DGE is a well-known complication after gastrojejunostomy, but again it was not significantly longer, while the occurrence of GOO, the primary end point, was highly significant.

After the publication of the trial from Hopkins, we discussed with the participating centers whether we should discontinue the trial early after the start. Together with our statistician, we decided to continue and to perform an interim analysis after 50% inclusion of the patients. Since the interim analysis showed similar results as in the Hopkins trial, we stopped including patients. By doing this, we might have introduced the possibility of a type II error, especially regarding the secondary endpoints as DGE and length of hospital stay. However, since both randomized trials showed a better outcome after a double bypass, we decided that it was not justified to continue the trial.

MR. R.C.G. RUSSELL: Did you assess the duodenum at the time of the operation? The number of people, that is 12, with delayed duodenum obstruction is high, compared with other series. The second question is: what were your indications for undertaking the delayed gastric bypass? Did you prescribe the usual prokinetic agents before you resorted to surgery? The third question is whether the patients were nearing the end or their life and would they not have been better treated by duodenal stents; these stents can be most effective and do not alter the management of these patients.

DR. N.T. VAN HEEK: To start with the last question. There are indeed surgeons who believe that a single bypass is sufficient, and that if GOO occurs, you still can place a duodenal stent, which is a less invasive procedure. Our group of patients had a survival prognosis of at least 6 months. We do not prefer placing duodenal stents as a primary treatment of patients with a life expectancy of more than 6 months because duodenal stents might occlude more easily than a gastrojejunostomy and these patients also need a biliary stent.

DR. A.G. JOHNSON: I am still worried that you had 34 patients with undiagnosed metastases. I am not sure you quite answered Dr. Neuhaus' question: what were your imaging techniques and did you do routine staging laparoscopy before operation to try and detect these? Secondly, I think you should continue with this trial; the American trial had very small numbers and there could still be an error from small numbers even with twice as many. I see no ethical reason why you should not continue because the quality of life is the same at the end of the time and all you are doing is relieving the obstruction at a different stage in some patients. You still do not have to operate on the majority for late obstructions. So I think you should continue.

DR. N.T. VAN HEEK: Thank you, Dr. Johnson, I appreciate your opinion. We do not perform diagnostic laparoscopy anymore preoperatively, as mentioned earlier after the previous trial on diagnostic laparoscopy. I agree on your argument that more significant differences between both groups could have come to light if we would have included 140 patients, especially considering DGE and length of hos-

pital stay. Again, as mentioned earlier, together with the participating centers and the statistician we decided to stop.

Dr. M.W. Büchler: The number of discussants tells you how important this study is. This is the kind of study that needs to be presented here at the ESA meetings. I find your study a very good study that has come to a conclusive end. Nothing better can happen than that a statistician tells you that you have to stop the study because you have a significant end point. My feeling is, this is excellent and I would not go on.

The other thing is that we have now two randomized controlled trials: yours and the one from Baltimore. Yours is multicenter, so it is even more important. Do you think that we should conclude that we should go on double bypass in the future or do you think that we have to run more of such trials?

Dr. N.T. van Heek: Thank you, Professor Büchler. As you, we have the opinion that sufficient evidence is shown to propagate the double bypass in patients with peripancreatic cancer, which turns out to be unresectable during explorative laparotomy, in particular because it does not increase morbidity and mortality significantly. In my opinion, no more trials are needed.

Dr. M. Morino: Following on the same line: do you believe that, as your study and the other study show that gastric outlet obstruction is so important, we should design a study of once again surgical palliation versus stenting even in a patients that are not resectable before surgery.

And you showed in another study that stenting is not as good as surgical bypass.

Dr. N.T. van Heek: I think there is no reason any more to perform such a study to compare stents with surgical palliative procedures. Patients with extensive disease should undergo a stenting procedure as shown previously because of the short life expectancy.

Dr. H.G. Gooszen: This is probably more of a remark or a suggestion: your study is another example of your group where quality of life was an integral part of the analysis and where you anticipated to find a major difference but did not. So probably you should go back to the Medical Psychology Group of Prof. De Haes and discuss this. There are so many other examples in the current literature, where one would anticipate to find a difference but failed. So I think that with the quality of life analysis we are doing as part of a lot of studies, with a lot of energy, we probably are not using the right instrument. What do you think?

Dr. N.T. van Heek: Thank you, Professor Gooszen. I agree. Of course, we discussed this study also with Professor Sprangers, and the Medical Psychology Department is working continuously on these questionnaires, and developing not only new ones, they are working also on cancer-specific modules, but again we indeed are surprised, and one would suggest that there is something wrong with the measurement we currently perform on quality of life assessment, I agree.

Dr. A. Fingerhut: My second comment is: the discussion here has been lively and passionate, especially as concerns whether the study should have been continued or not. Let me just add a comment which need not be answered. This study has used a methodology which I am quite fond of, that is, you have given us the number needed to treat. This means that you have added clinical significance to the statistical significance of the results of the study. Thank you for that and, once again, congratulations on this excellent paper.